REMARKS

Upon entry of these amendments, claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are pending in the present application. Claims 55-72 are withdrawn. Claims 1, 35 and 53 are amended to more clearly define the invention. No new matter is added.

Double Patenting Rejections

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are provisionally rejected under the judicially created doctrine of obvious-type double patenting, as being unpatentable over claims contained within U.S. Patent Application Nos. 10/866,751, 10/887,009, 10/995,565, 11/068,459, 11/069,637 and 11/201,097. Applicants will review these pending applications as requested by the Examiner and will consider filing a terminal disclaimer upon notice of allowable subject matter in these applications or the instant application.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. *See*, Office Action at pages 2-5. Applicants traverse with respect to the pending claims as amended herein.

The Examiner states that the specification fails to provide written support for claims the determination of a dosage of a checkpoint activator via measuring the "unscheduled expression" of an E2F transcription factor, as previously recited in claims 1 and 35. *See*, Office Action at page 3. As amended herein, claims 1 and 35 no longer recite "unscheduled expression" or the determination of a dosage by measuring the unscheduled expression of a member of the E2F family of transcription factor.

Applicants show possession of the claimed invention at least at page 34 lines 1-7 and at Table 1 at page 33. Table 1 shows the effects of several checkpoint activators on various cells lines of Prostate, Colon, Breast, Pancreas and Lung cancers and corresponding non-cancerous cell lines. The table also shows the effects of the activators on the E2F induction. Table 1

clearly shows that when E2F is activated, cancer cell lines are reduced, while normal cell lines are maintained. As such, the Applicant shows possession of the claimed invention.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are also rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the administration of a dose that selectively activates a checkpoint in cancerous cells but does not affect the cytotoxicity or viability of non-cancerous cells. *See*, Office Action at pages 5-6. Applicants traverse with respect to the pending claims as amended herein.

As stated above, Applicants have amended claims 1, 35 and 53 (from which the remaining claims depend), so that they no longer recite determining the appropriate dosage of the checkpoint activating compound by measuring the unscheduled expression of a member of the E2F family of transcription factors.

The claims, as amended herein, recite that a checkpoint activator is administered such that the E2F family of transcription factors is elevated, as shown in Table 1, Example 2 and Figures 7-11.

Therefore, Applicants submit that one of ordinary skill in the art would be able to make and use the invention as claimed and amended herein. Reconsideration and withdrawal is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1, 4-5, 9-17, 35, 38-39, 43-51 and 73-74 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, specifically what is meant by the phrase "unscheduled expression of a member of the E2F family of transcription factors." *See*, Office Action at page 9.

Although Applicants submit that the instant application sufficiently describes the meaning of "unscheduled expression of a member of the E2F family of transcription factors"

such that one of ordinary skill in the art would reasonably be apprised of the metes and bounds of the claimed subject matter, to facilitate prosecution, Applicants have amended claims 1 and 35, from which the remaining claims depend, to no longer recited unscheduled expression of a member of the E2F family of transcription factors. Therefore, this rejection is moot and should be withdrawn.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are also rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, specifically, the limitation "but not affect the cytotoxicity or viability of non-cancerous cells."

Applicants have amended claims 1, 35 and 53 so that they no longer use the word cytotoxicity, but rather use the word "toxic" so that it is clear that Applicant intends to claim the at the checkpoint activator is administered such that the checkpoint is activated in cancerous cells but is not toxic to non-cancerous cells and, thus, does not affect their viability. As such, Applicant respectfully requests that this rejection be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 6,875,745 to Pardee ("Pardee") in view of the article, Dyson, et. al., "The Regulation of E2F by pRB-Family Proteins", *Genes and Development*, 12:2245-2262; 1998 ("Dyson"). Applicants traverse the rejection with respect to the pending claims as amended herein.

The Examiner has stated that Pardee teaches a method for treating a mammalian tumor by administering a G1 and/or S phase drug, preferably the topoisomerase I inhibitor beta-lapachone or a derivative or analog of beta lapachone, in combination with a G2/M phase drug. Additionally Pardee states that "molecular changes underlying cell cycle delay at multiple checkpoints, e.g., G1 and/or S phase and G2/M phase, can result in the synergistic induction of apoptosis in malignant cells. *See*, Office Action at page 11.

Claims 1, 35 and 53, as amended herein and from which the remaining claims subject to the rejection depend, recite a method of administering a G1 and/or S phase checkpoint activator so that the expression of a member of the E2F family of transcription factors, selected from E2F-1, E2F-2, and E2F-3 is elevated and activates a checkpoint in cancerous cells but is not toxic to and does not effect the viability of non-cancerous cells. Pardee does not teach or suggest the E2F family of transcription factors. Additionally, Pardee does not teach or suggest administering a checkpoint activator so that the expression of a member of the E2F family of transcription factors is elevated in cancerous cells leading to apoptosis/cell death, but is not toxic to and does not effect the viability of non-cancerous cells.

Dyson does not cure the deficiencies of Pardee. Dyson generally teaches that E2F transcription proteins play an important role in cell proliferation and differentiation. Dyson states that "E2F regulation differs greatly depending whether cells are moving from M to G_1 to S phase or from G_0 to G_1 to S phase." See, pages 2250-2251, column 2 and column 1, respectively.

It appears that the Examiner is suggesting that since molecular changes in the cell cycle cause delays at multiple checkpoints, which can result in the induction of apoptosis in malignant cells, it would have been obvious for one of ordinary skill in the art to screen for the E2F family of transcription proteins because it is a cell cycle protein. This is clearly a rejection based on an obvious-to-try standard which is not permitted.

The admonition that obvious to try is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it (Emphasis Added). *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The only motivation or guidance in the prior art that the Examiner has asserted is that cell cycle proteins that induce apoptosis in malignant cells could be tried in a rubric of routine experimentation. Specifically, Pardee only provides that "molecular changed underlying cell cycle delay at multiple checkpoints, for example G1 and/or S phase and G2/M phase, can for example result in synergistic induction of apoptosis in malignant cells" (Emphasis Added). *See*, Office Action at page 11.

The "as a whole" instruction in 35 U.S.C. § 103 prevents evaluation of the invention part by part. *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270 (Fed. Cir. 2004). Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. *Id.* This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention. *Id.* Thus, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor (Emphasis Added). *Id.* When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination. *Id.*

Using references available on the filing date of the instant application, an innumerable amount of cell cycle proteins exist, e.g., cyclins, cyclin-dependent kinases, (cdks), cell division cycle proteins (cdcs), p53, p27(kip1), p21 (cip1/waf1), SCF (Skp2), retinoblastoma proteins, etc.

Based on the teachings in the art, a skilled artisan would recognize that the experimentation necessary to find and use the drugs of Pardee and the E2F transcription factors of Dyson would not have been routine. In fact, to use the E2F transcription factors of Dyson referred to by the Examiner, without the teachings of the instant application, one of ordinary skill in the art would have to try most or all of the available cell cycle proteins and following the test in *In re O'Farrell* to try each of numerous possible choices until one possibly arrived at a

successful result an impermissible standard for assessing obviousness (853 F.2d 894, 903). Applicants submit that reaching the claimed invention without the teachings of the instant application would involve more than routine experimentation, and for each cell cycle protein tested, would not have a reasonable expectation of success. Therefore, Applicants submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Pardee and Dyson to reach the presently claimed invention.

Moreover, claims 1, 35 and 53 as amended herein specifically recite a checkpoint activator that is an compound with a molecular weight of less than 5 kD, which does not damage DNA and does not stabilize microtubules and is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein the checkpoint activator is not toxic to and does not effect the viability of non-cancerous cells.

Pardee does not discuss a checkpoint activator with any of the qualities as stated above, especially that the checkpoint activator elevates the expression E2F family of transcription factors but also is not toxic to and does not effect the viability of non-cancerous cells. Dyson does not cure the deficiencies of Pardee. Dyson states, "E2F is regulated in a cell dependent manner and fluctuations in E2F activity enable programs of gene expression to be coupled closely with cell cycle position...Further studies have shown that activation of E2F-dependent transcription promotes cell cycle progression and S-phase entry." *See*, Office Action at pages 11 and 12. Dyson does not teach or suggest the elevation in expression of the E2F family of transcription factors in cancerous cells while remaining not toxic to and not effecting the viability of non-cancerous cells. As such, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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